Drug's 'double hit' overcomes leukaemia resistance

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A drug that uses a unique ‘double hit’ to kill leukaemia cells could be a potential new treatment for patients with acute myeloid leukaemia. The research, majority funded by Cancer Research UK, is published this week in Leukaemia.

Around 30 per cent of patients with AML have faults in the FLT3 gene, which are linked to more aggressive leukaemias and poor survival. While drugs that target these faults are available, the disease eventually builds

resistance, leaving treatments ineffective.

To combat this, researchers at The Institute of Cancer Research (ICR) in London, funded by Cancer Research UK and Breakthrough Breast Cancer, developed a unique drug that targets AML cells in a "double hit". The drug blocks the protein made by the faulty FLT3 gene along with another key protein – called Aurora kinase – which are both involved in driving cancer growth.

In healthy blood cells, FLT3 sends a signal to the cells telling them when to proliferate, while Aurora kinase plays a role in cell division. Leukaemia cells with faulty FLT3 can proliferate out of control, while many cancer cells have higher levels of Aurora kinase, causing errors during cell division. This 'double hit' drug blocks both mechanisms that otherwise promote leukaemia growth.

The drug is also unique because it can destroy cells even if they develop new faults in the FLT3 genes that would make them resistant to other inhibitors.

The combination led to complete remission in half of the mice treated with this drug, compared with only 25 per cent with an existing drug that only blocks FLT3.

Lead author Dr. Spiros Linardopoulos, leader of the Cancer Drug Target Discovery Team at The Institute of Cancer Research said: "There has been great interest in using FLT3 drugs to treat AML, but their effectiveness has been limited because leukaemia cells gain new mistakes in the FLT3 gene, causing resistance.

"Our new drug has the potential to overcome this and has a range of possible uses in AML – as a first line of attack for patients with faulty FLT3, in particular in those over 60 who don't tolerate chemotherapy

well, and also to treat leukaemia patients who have relapsed."

Professor Paul Workman, director of the Cancer Research UK Cancer Therapeutics Unit at The Institute of Cancer Research, said: "We're excited about the potential of our new 'double hit' drug and are now planning to take it into clinical trials to see if it is effective in patients."

The faults that occur in the FLT3 gene cause rapid cell division, and one particular mistake is linked to a very poor outcome in both adults and children with AML. Each year around 2,380 people are diagnosed with AML in the UK.

Dr. Julie Sharp, senior science information manager at Cancer Research UK, said: "Cancer Research UK has a long history of developing drugs to treat leukaemia more effectively. But designing treatments that overcome resistance is a major challenge for researchers.

"By creating cells in the lab that mimic how drug resistance develops in AML the researchers were able to show that their new drug delivers a 'double hit' to halt cancer cells in their tracks. Next they will test the new drug in patients to see if it has the potential to treat people with aggressive AML."

More information: Moore AS (2012). Selective FLT3 inhibition of FLT3-ITD(+) acute myeloid leukaemia resulting in secondary D835Y mutation: a model for emerging clinical resistance patterns. Leukemia , 26 (7) PMID: 22354205

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